REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. AMENDMENTS TO THE SPECIFICATION AND SUBMISSION OF SEQUENCE LISTING

In the specification, a sequence listing has been added to the application (as was required in the child application) and paragraphs have been amended to insert the required sequence identifiers associated with each listed sequence. No new matter is entered.

II. AMENDMENTS TO THE CLAIMS

Claims 1, 5, and 47-48 are currently being amended.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. No new matter has been added.

After amending the claims as set forth above, claims 1, 5-7, 9-12, 27-28, 30, 39, and 47-48 are under examination in this application. Claims 15-17, 21-24, 29, 31-38, and 40-46 stand withdrawn as non-elected.

III. OBJECTION AND INFORMALITY

Applicants have amended claims 1 and 48 as suggested by the Office to insert "*Lac*" before "Z^-Y^+."

Applicants have replaced "sulfatation" with "sulfation" in claim 5 (the Office had suggested such correction, referring to "claim 2" in error).

IV. REJECTION UNDER § 112 (INDEFINITENESS)

Applicants have replaced "or" with "and" in claim 47, as suggested by the Office.

Regarding "sialic acid", the Office stated, "[I]t is unclear under what conditions lactose permease will internalize sialic acid" (Office Action, page 3, lines 3-5). To further prosecution and obviate this ground of rejection, Applicants have amended claim 47 to recite "lactose permease or NanT permease." As noted in the specification, when the "precursor is sialic acid . . . active transport of said precursor is performed by NanT permease" (specification, page 14, lines 6-8).

V. REJECTIONS UNDER § 103(A) (OBVIOUSNESS)

The Office has rejected claims 1, 5-7, 9-12, 27-28, 39, and 47-48 over the combination of Bettler and Kosumi. The Office has rejected claim 30 over Bettler, Kosumi, and WO 96/10086.

Applicants respectfully traverse, because (A) Bettler is not prior art and (B) even if Bettler were prior art, the invention as claimed would be nonobvious over the combinations of references. In support, Applicants submit herewith an unexecuted Declaration under 37 C.F.R. § 1.132 by Dr. Eric Samain ("Samain Declaration"). An executed version will follow soon.

A. Bettler Is Not Prior Art

The obviousness rejections are defective and must be withdrawn, because the Bettler reference upon which both rejections are based is not prior art to the present invention as claimed.

The Office must consider evidence to establish the date when a publication became publicly accessible. See M.P.E.P. § 2128.02 ("Specific evidence showing when the specific document actually became available is not always necessary") (citing *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560 (evidence showing how documents were usually treated sufficed to show when specific documents were accessible to the public) and *In re Hall*, 781 F.2d 897 (Fed. Cir. 1986).

While the Office does not require evidence regarding a specific reference, Applicants provide herewith specific evidence of the publication date of Bettler. Bettler was published on September 24, 1999. As evidence for this assertion, Applicants refer to the attached Samain Declaration and the attached letter from Springer Science & Business Media, the publisher of Bettler. The Samain Declaration refers to the Springer letter, which was addressed to the Declarant (see Samain Declaration, page 4, paragraphs 6-7). The Springer letter states that while Bettler appeared in a Glycoconjugate Journal issue that was labeled as "March 1999" the actual print publication date of Bettler was September 24, 1999, and Bettler appeared online on SpringerLink years later on October 28, 2004.

Applicants have attached herewith a certified copy of the French priority document FR 99 08772 filed July 7, 1999. This submission perfects Applicants' claim of priority to the date July 7, 1999.

Accordingly, Bettler has a publication date after the priority date of the claims under examination and should not be considered as prior art. Both obviousness rejections depend on Bettler as primary prior art reference and, with Bettler removed as prior art, must be withdrawn as deficient.

B. Even Considering Bettler As Prior Art, The Claims Are Nonobvious

The Office must consider "all rebuttal arguments and evidence presented by applicants." M.P.E.P. § 2145 (citing *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (error not to consider evidence presented in the specification) and *In re Beattie*, 974 F.2d 1309, 1313, (Fed. Cir. 1992) (Office should consider declarations by skilled artisans praising the claimed invention and opining that the prior art teaches away)).

Applicants submit that the claims are nonobvious, because (1) the Office has mischaracterized Dykhuizen, (2) the specification demonstrates unexpected results of the invention, and (3) the prior art would not led a skilled artisan to the invention as claimed. In support, Applicants refer to the Samain Declaration.

1. The Office has mischaracterized Dykhuisezn

The Office cited Dykhuizen for the following premise:

> lactose killing . . . is present in E. coli cells that have been growing on a limited supply of lactose when they were then provided with excess lactose but not in cells growing on other carbons sources when supplied with lactose."

2008 Office Action, page 4 (emphasis in original). As explained in the Samain Declaration, the Office's interpretation of Dykhuizen contradicts directly relevant disclosures within Dykhuizen. The Samain Declaration states that lactose cells grown on other carbon sources experience no lactose killing because the lactose permease in those cells has not been induced, given the absence of lactose. Samain Declaration, page 5, paragraph 9. As further stated in the Samain Declaration, Dykhuizen discloses a strong correlation between lactose permease levels and the amount of lactose killing:

> On the contrary as shown in table 2 of Dykhuisezn [sic] et al., cultivation of E. coli cells on glucose or galactose in presence of IPTG (which is an inducer of the lactose permease) results in a strong lactose killing effect. The authors conclude (on page 878, column 2, line 11-17) that **" there is strong correlation between the amount of lactose permease and the amount of lactose killing."**

Samain Declaration, page 5, paragraph 10. Consequently, the Office's rejection is based on an interpretation of Dykhuzen that the reference itself contradicts.

2. The invention yields unexpected results

The Samain Declaration refers to evidence of unexpected results in production of complex oligosaccharides at a concentration of more than 25 g/l via the invention as claimed. Samain Declaration, pages 5-6, paragraph 13.

The Office has stated that "the amount of growth inhibition produced by lactose can be diminished by reducing the rate of import of lactose into the cells and the presence of glucose or glycerol in the culture during the second phase of cell growth would do just that as they are well know to repress the lactose promoter" (2008 Office Action, page 5).

As noted in the Declaration, however:

> It is true that glucose (but not glycerol) represses the lactose promoter by a mechanism called catabolic repression. However, in the invention as claimed, the second phase of cell growth is carried out in carbon-limiting condition to precisely prevent this catabolic repression and enable the full expression of the lactose permease, which is a necessary condition for a very efficient system of oligosaccharide synthesis. One should keep in mind that the interest of this invention is its very high productivity and that we have later succeeded in obtaining by the process as claimed the production of complex oligosaccharides at a concentration of more than 25 g/l (see publication Fierfort and Samain – J. of Biotechnology, 2008, in exhibit C).

Samain Declaration, pages 5-6, paragraph 13. Applicants have attached a copy of the cited reference Fierfort and Samain, J. of Biotechnology 134 (2008) 261-265. The Declaration explains why this result would have been unexpected to skilled artisans (Samain Declaration, page 6, paragraphs 14-15):

> 14. A skilled artisan in this field would not have anticipated such excellent results. On the contrary, the skilled artisan would have considered that there was no industrial interest in developing a process whose yield would be limited by the lactose input due to the lactose killing effect. Thus, a skilled artisan would not have contemplated using a system as defined in the claims.
>
> 15. In addition, the lactose promotor and other catabolically repressed promotor such as the arabinose promotor are largely used in common expression vector and in particular in almost all the expression vectors that were used in the examples of the claimed invention to overexpress the genes for glycosyltransferases and other enzyme involved in sugar nucleotide biosynthesis that are required for the synthesis of complex oligosaccharides. Therefore, one skilled in the art would not have considered the process as claimed since partial repression by catabolic repression of the lactose promotor would affect not only the expression of the lactose permease but also the expression of other genes involved in oligosaccharide synthesis.

The unexpected results provided by the invention as claimed would overcome any prima facie case, if such could be made out in view of the disqualification of Bettler as prior art.

3. The prior art would not have led a skilled artisan to the invention as claimed

The Samain Declaration presents further evidence that a skilled artisan would not have been led to the invention, such that the present claims could not be properly considered obvious. For example, the Declaration states that while the Office asserted that "even a low growth rate of the cells during the second phase could still be sufficient to produce large amount of the desired product" (2008 Office Action, page 5) the primary concern is "not the problem of slow growth but more the problem of irremediable damage to the cells, which would affect their metabolically activity and their energetic yield" (Samain Declaration, page 7, paragraph 17).

Also, the Declaration notes that LacZ+ strain used in reference Dykhuizen means that the corresponding cells hydrolyze and catabolize lactose, while the present invention relates to LacZ- strains such that:

> the lactose accumulates intracellularly at high concentration. A skilled artisan would have feared that this accumulation could be detrimental for the cells by dramatically increasing the intracellular osmotic pressure (turgor). This increase in turgor can cause cell death because of membrane rupture, and bacterial cells are known to adapt to severe turgor increase by opening stretch activated channel to let small molecule exit. As a small molecule lactose is likely to exit through the activated channel and to create an energy consuming futile cycle by being reinternalized by the lactose permease.

Samain Declaration, page 7, paragraphs 18-19.

Moreover, the Declaration explains that the present invention would not have been obvious to a skilled artisan because such a skilled artisan would have been more motivated to improve the processes disclosed in Bettler or Koizumi rather than pursue another approach, given that "the accumulation of any metabolite is susceptible to be toxic for a cell, and the lactose killing effect is a well-known phenomenon." Samain Declaration, page 7, paragraph 21.

For all the reasons given above, Applicants respectfully request that the Office withdraw the rejections under § 103(a) for obviousness.

VI. PROVISIONAL NONSTATUTORY DOUBLE PATENTING

The Office has provisionally rejected all claims under examination except claim 30 for nonstatutory obviousness-type double patenting over copending Application Nos. 11/447,287 and 11/509,818.

Applicants request the Office to maintain this ground of rejection in abeyance pending indication of allowable subject matter.

VII. CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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